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STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/695,065	BRASCH ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-20, 27, and 30-57* is/are pending in the application.

4a) Of the above claim(s) *40-43 and 52-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-20, 27, 30-39, 44-51, 56, and 57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6/03, 7/03, 10/03
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of species (2) (claims 34-39 and 47-51) filed on October 10, 2003 is acknowledged. The traversal is on the ground(s) that "even where patentably distinct inventions appear in a single application, restriction remains improper unless the Examiner can show that the search and examination of the groups would entail a 'serious burden.' See MPEP § 803. In the present situation, the Examiner has failed to make such a showing.".

The above arguments have been fully considered but they have not been found persuasive toward the withdrawal of the restriction requirement nor persuasive toward the relaxation of same such that all species will be examined together. First, species (1)-(10) are different recombination sites and are required different searches. For example, a search required for species (1) such as lox p is not required for other species such as attB (species 2). Therefore, there is a burden on the examiner to search all species together. Second, according to MPEP § 809.02(a), "[S]hould applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.". However, applicant does not submit evidence or identify such evidence now of record showing the species (1) and (3)-(10) to be obvious variants of species (2) or clearly admit on the record that this is the case.

Therefore, the requirement is still deemed proper and is therefore made FINAL and claims 14-20, 27, 32-39, 44-51, 56, and 57 will be examined.

Claim Objections

2. Claim 14 is objected to because of the following informality: "recombination sites" in transferring step should be "at least one recombination site" in order to correspond to inserting step of the claim.

3. Claims 15 and 27 are objected to because of the following informality: "genomic, chromosomal" should be "genomic DNA, chromosomal DNA".

4. Claim 16 is objected to because of the following informality: "at least a first and a second recombination site" in inserting step should be "at least a first and a second recombination sites" in order to correspond to "said at least a first and a second recombination sites" in the claim.

5. Claims 34-37 are objected to because of the following informality: "claims 30-33" should be "claims 32 and 33" since claims 30 and 31 have been canceled by applicant.

6. Claims 34, 35, and 47 are objected to because of the following informality: "a eukaryotic organism" should be "an eukaryotic organism"

7. Claim 16 is objected to because of the following informality: (1) "at least a first and a second recombination site" should be "at least a first and a second recombination sites"; and (2) "at least a third and a fourth recombination site" should be "at least a third and a fourth recombination sites" in the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 14 is rejected as vague and indefinite because it is unclear whether "at least one nucleic acid molecules" in inserting step and "one or more nucleic acid molecules" in transferring step are identical or not since the claim does not describe the relationship between "at least one nucleic acid molecules" and "one or more nucleic acid molecules". Please clarify.

11. Claim 15 is rejected as vague and indefinite. Since claim 14 has "at least one nucleic acid molecule" and "one or more nucleic acid molecules", it is unclear that "said nucleic acid molecule" in claim 15 means "at least one nucleic acid molecule" or "one or more nucleic acid molecules". Please clarify.

12. Claim 18 is rejected as vague and indefinite. Since claim 16 has "at least one nucleic acid molecule" and "a nucleic acid molecule", it is unclear that "said nucleic acid molecule" in claim 18 means "at least one nucleic acid molecule" or "a nucleic acid molecule". Please clarify.

13. Claim 32 recites the limitation "said first and second recombination sites" in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no phrase "first and second recombination sites" in claim 14. Please clarify.

14. Claims 34 and 35 are rejected as vague and indefinite. Since claims 32 and 33 have a first and a second recombinant sites, it is unclear that "said recombination sites" in claims 32 and 33

mean a first and a second recombinant sites or mean the first recombination sites or mean the second recombination sites in claims 34 and 35. Please clarify.

15. Claims 46-49 are rejected as vague and indefinite. Since claim 44 has a first recombination site, a second recombination site, a third recombination site, and a fourth recombination site, it is unclear that which above recombination sites in claim 44 mean "said recombination sites" in claims 46-49. Please clarify.

16. Claim 56 recites the limitation "said second nucleic acid comprising said first segment" in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no second nucleic acid comprising said first segment in claim 44 and a second nucleic acid comprising said first segment is not equal to the second nucleic acid recited in claim 44. Please clarify.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (c) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (f) he did not himself invent the subject matter sought to be patented.

18. Claims 14-20, 27, 32, 33, 44-46, and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Stemmer (US Patent No. 5,605,793, published by February 25, 1997).

Stemmer teaches method for *in vitro* recombination which can be used in many different genes encoded proteins.

Regarding claim 14, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein" is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Stemmer teaches inserting one or more double-stranded oligonucleotides comprising one or more mutations into double-stranded random fragments, denaturing the resultant mixture of the double-stranded random fragments and oligonucleotides into single-stranded fragments, incubating the resultant population of single-stranded fragments with a polymerase under conditions which results in the annealing of said single-stranded fragments at regions of identity between the single-stranded fragments and formation of a mutagenized double-stranded polynucleotide (see column 3, second paragraph). Since one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer is capable of inserting randomly into a target nucleic acid molecule (ie., one or more double-stranded random fragments), one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer is one or more integration sequences as recited in

claim 14. Since one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer are inserted into one or more double-stranded random fragments in the presence of a polymerase and form a mutagenized double-stranded polynucleotide, one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer contain one or more recombination sites as recited in claim 14. Therefore, Stemmer discloses inserting one or more integration sequences (ie., one or more double-stranded oligonucleotides comprising one or more mutations) comprising at least one recombination site into at least one nucleic acid molecule (ie., double-stranded random fragments) as recited in claim 14. Since the mutagenized double-stranded polynucleotide taught by Stemmer is cloned into an appropriate vector (see column 8, lines 60 and 61) and it is known that a cloning process must used a ligase, according to the definition of "recombination protein" in the specification, a ligase is a recombination protein and Stemmer discloses transferring one or more nucleic acid molecules formed in the inserting step comprising at one recombination site into one or more vectors in the presence of one or more recombination proteins (ie., a ligase) as recited in claim 14.

Regarding claims 16 and 18, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Stemmer teaches inserting one or more double-stranded oligonucleotides

comprising one or more mutations into double-stranded random fragments, denaturing the resultant mixture of the double-stranded random fragments and oligonucleotides into single-stranded fragments, incubating the resultant population of single-stranded fragments with a polymerase under conditions which result in the annealing of said single-stranded fragments at regions of identity between the single-stranded fragments and formation of a mutagenized double-stranded polynucleotide (see column 3, second paragraph). Since one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer is capable of inserting randomly into a target nucleic acid molecule (ie., one or more double-stranded random fragments), one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer is one or more integration sequences as recited in claim 16. Since one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer are inserted into one or more double-stranded random fragments in the presence of a polymerase and form a mutagenized double-stranded polynucleotide, one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer contain one or more recombination sites as recited in claim 16. Therefore, Stemmer discloses inserting one or more integration sequences (ie., one or more double-stranded oligonucleotides comprising one or more mutations) comprising at least one recombination site into at least one nucleic acid molecule (ie., double-stranded random fragments) as recited in claim 16. Since, after restriction digestion, the digested mutagenized double-stranded polynucleotide taught by Stemmer is cloned into an appropriate vector (see column 8, lines 60 and 61 and column 12) and it is known that a cloning process must used a ligase, according to the definition of "recombination protein" in the specification, the digested mutagenized double-stranded

polynucleotide taught by Stemmer is a nucleic acid comprising at least a first and a second recombination site as recited in claim 16 wherein 5' and 3' ends of restriction sites of the digested mutagenized double-stranded polynucleotide are a first and a second recombination site and Stemmer discloses causing said at least first and second recombination sites to recombine in the presence of at least one recombination protein (ie., a ligase) as recited in claim 16. Since Stemmer teaches that 5' and 3' ends of restriction sites of the digested mutagenized double-stranded polynucleotide are a first and a second recombination site, Stemmer discloses that said first and second recombination sites are separated by a portion of a nucleotide sequence as recited in claim 18.

Regarding claims 15 and 27, since double-stranded random fragments are generated from a PCR product of the wild-type LacZ alpha gene (see column 11), the double-stranded random fragments are genomic DNA as recited in claims 15 and 27.

Regarding claim 17, since an appropriate vector taught by Stemmer is a plasmid such as pUC 18 (see column 12, lines 13-67) and it is known that a plasmid is a circular molecule, Stemmer discloses that said recombination of said first and second recombination sites insert into the vector and results in a circular molecule as recited in claim 17.

Regarding claims 19 and 20, since the oligonucleotides comprising one or more mutations taught by Stemmer can be single stranded and it is known that a single stranded nucleic acid can be labeled with P^{32} at the 5' end in the presence of T4 polynucleotide kinase. According to the definition of "selectable markers" in the specification (see page 26, last paragraph bridging to page 27, first paragraph), selectable markers are DNA segments that bind products that modify a substrate, the oligonucleotides comprising one or more mutations taught

by Stemmer are DNA segments that bind product that modify a substrate (ie., T4 polynucleotide kinase) or one or more selective markers as recited in claims 19 and 20.

Regarding claims 32 and 33, since Stemmer teaches that said first and second recombination sites are 5' and 3' ends of restriction sites (see above), Stemmer discloses that said first and second recombination sites are site-specific recombination sites as recited in claims 32 and 33.

Regarding claim 44, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Stemmer teaches to digest a PCR product with restriction enzymes BamHI and Eco0109 and ligates digested PCR product into pUC18 digested with BamHI and Eco0109 (see column 12, lines 6-67). Since 3' and 5' of the digested PCR product taught by Stemmer has restriction sites, Stemmer discloses a first nucleic acid molecule comprising at least a first segment which comprises at least a first and a second recombination site (ie., 3' and 5' restriction sites of the digested PCR product), wherein said segment comprises at least one integration sequence as recited in step (a) of claim 44. Since 5' and 3' ends of pUC18 contain restriction sites, Stemmer discloses a second nucleic acid molecule comprising at least a third and fourth recombination site (ie., 5' and 3' restriction sites of pUC18) as recited in steps (b)

and (c) of claim 44. Since, during the ligation reaction, the digested PCR product must mix with pUC18 digested with BamHI and Eco0109 in the presence of a ligase, Stemmer discloses forming a mixture by mixing said first nucleic acid molecule (ie., the digested PCR product with at least one second nucleic acid molecule comprising at least a third and fourth recombination site (ie., pUC18 digested with BamHI and Eco0109) in the presence of at least one recombination protein (ie., a ligase) and incubating said mixture under conditions favoring recombination at least between said first (ie., the BamHI site on the digested PCR product) and third recombination sites (the BamHI site on the digested pUC18) and at least between said second (ie., the Eco0109 site on the digested PCR product) and fourth recombination sites (ie., the Eco0109 site on the digested pUC18), thereby transferring said first segment (ie., the digested PCR product) from said first nucleic acid molecule to said second nucleic molecule (ie., the digested pUC18) as recited in steps (b) and (c) of claim 44.

Regarding claims 45 and 46, since 3' and 5' of the digested PCR product taught by Stemmer has restriction sites (see above), Stemmer teaches that said first segment (ie., the digested PCR product) is flanked on one side by said first recombination site and is flanked on the other side by said second recombination site as recited in claim 45 wherein said recombination sites are site-specific recombination sites as recited in claim 46.

Regarding claim 57, since the ligation reaction taught by Stemmer is performed in *in vitro* (see column 12, lines 6-67), Stemmer discloses that said recombination (ie., the ligation taught by Stemmer) takes place *in vitro* as recited in claim 57.

Therefore, Stemmer teaches all limitations recited by claims 14-20, 27, 32, 33, 44-46, and 57.

Response to Arguments

In page 8, second paragraph bridging to page 9, first paragraph of applicant's remarks, applicant argued that: (1) "[S]temmer does not disclose an operative method for the insertion of one or more integration sequences into a nucleic acid molecule in the presence of one or more recombination proteins; and (2) "[S]temmer contains no disclosure of the use of recombination proteins as recited in the present claims.".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, claim 14 requires one or more recombination proteins in transferring step while claim 16 requires one or more recombination proteins in causing step. Claims 14 and 16 do not require that the insertion of one or more integration sequences into a nucleic acid molecule is performed in the presence of one or more recombination proteins (see claims 14 and 16). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Second, since "recombinant protein" is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph), the ligase taught by Stemmer is a recombination protein. Therefore, Stemmer contains disclosure of the use of recombination proteins as recited in claims 14 and 16.

19. Claims 14-20 , 27, 32, 33, 44-46, and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Atlung *et al.,* (Gene 107, 11-7, October 1991).

Atlung *et al.*, teach a versatile method for integration of modified genes and gene fusions into the bacteriophage lambda attachment site (attB) of the *Escherichia coli* chromosome.

Regarding claim 14, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Atlung *et al.*, teach to construct plasmid pTAC3599 by cloning a 740-bp Taq I fragment containing the promoter appYp into the Sama I site of pTAC3575 (see Figure 1 in page 12). Since the restriction sites of the 740-bp Taq I fragment containing the promoter appYp is recombination sites, Atlung *et al.*, disclose inserting one or more integration sequences comprising at least one recombination site (ie., the 740-bp Taq I fragment containing the promoter appYp) into at least one nucleic acid molecule (ie., pTAC3575) as recited in claim 14. Since Atlung *et al.*, teach to ligate the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion to the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463 (see page 13, left column and Figure 2 in page 14) and it is known that a ligation reaction must be performed in the presence of a ligase, Atlung *et al.*, disclose transferring one or more nucleic acid molecules (ie., the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) comprising recombination sites (ie., restriction sites of the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA

gene and the appYp-lacz fusion) into one or more vectors (ie., the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463) in the presence of one or more recombination proteins (ie. the ligase) as recited in claim 14.

Regarding claims 16 and 18, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Atlung *et al.*, teach to construct plasmid pTAC3599 by cloning a 740-bp Taq I fragment containing the promoter appYp into the Sama I site of pTAC3575 (see Figure 1 in page 12). Since the restriction sites of the 740-bp Taq I fragment containing the promoter appYp is recombination sites, Atlung *et al.*, disclose inserting one or more integration sequences comprising at least one recombination site (ie., the 740-bp Taq I fragment containing the promoter appYp) into at least one nucleic acid molecule (ie., pTAC3575) as recited in claim 16. Since Atlung *et al.*, teach to ligate the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion to the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463 (see page 13, left column and Figure 2 in page 14) and it is known that a ligation reaction must be performed in the presence of a ligase, a nucleic acid molecule that is produced by inserting one or more integration sequences comprising at least one recombination site (ie., the 740-bp Taq I fragment containing the promoter appYp) into at least

one nucleic acid molecule (ie., pTAC3575) and has the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion taught by Atlung *et al.*, comprising at least first (ie., BstE II site) and a second recombination sites (ie., Xho I site) as recited in claim 16 and Atlung *et al.*, disclose causing said at least first and second recombination sites (ie., BstE II and Xho I sites of the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) to recombine in the presence of at least one recombination protein (ie., the ligase) as recited in claim 16. Since the restriction sites of the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion taught by Atlung *et al.*, are located on 5' and 3' ends of the fragment, Atlung *et al.*, disclose that said first and second recombination sites are separated by a portion of a nucleotide sequence as recited in claim 18.

Regarding claims 15 and 27, since the purified BstE II-Xho I fragment of pTAC3599 carries the phoA gene and the appYp-lacz fusion, Atlung *et al.*, disclose that said nucleic acid molecule is genomic DNA as recited in claims 15 and 27.

Regarding claim 17, Since Atlung *et al.*, teach to ligate the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion to the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463 and generate a ligated circular molecule (see page 13, left column and Figure 2 in page 14), Atlung *et al.*, disclose that said recombination of said first and second recombination sites results in a circular molecule as recited in claim 17.

Regarding claims 19 and 20, since the integration sequences comprising at least one recombination site (ie., the 740-bp Taq I fragment containing the promoter appYp) taught by

Atlung *et al.*, has an appYp (acid phosphatase transcriptional activator gene, see left column in page 11), according to the definition of "selectable markers" in the specification (see page 26, last paragraph bridging to page 27, first paragraph), Atlung *et al.*, disclose that said integration sequence comprises one selectable marker (ie., appYp) as recited in claims 19 and 20.

Regarding claims 32 and 33, since Atlung *et al.*, teaches that said first and second recombination sites are 5' and 3' ends of restriction sites (ie., BstE II and Xho I sites) (see above), Atlung *et al.*, discloses that said first and second recombination sites are site-specific recombination sites as recited in claims 32 and 33.

Regarding claim 44, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Since Atlung *et al.*, teach to generate the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion, Atlung *et al.*, disclose obtaining a first nucleic acid molecule comprising at least a first segment (ie., purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) which comprises at least a first and a second recombination site (ie., BstE II and Xho I sites) wherein said segment comprises at least one integration sequence as recited in step (a) of claim 44. Since Atlung *et al.*, teach the purified BstEII-Sal I fragment carrying the attP-aphA cassette from

pTAC3463, Atlung *et al.*, disclose a second nucleic acid molecule comprising at least third and fourth recombination sites (ie., BstEII and Sal I sites) as recited in step (b) of the claim. Since, during the ligation reaction, the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion must mixed with the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463 in the presence of a ligase, Atlung *et al.*, disclose forming a mixture by mixing said first nucleic acid molecule (ie., the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) with at least one second nucleic acid molecule comprising at least a third and fourth recombination site (ie., the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463) in the presence of at least one recombination protein (ie., the ligase), and incubating said mixture under conditions favoring recombination at least between said first (ie., BstE II site from the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) and third recombination sites (ie., BstE II site from the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463) and at least between said second (ie., Xho I site from the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) and fourth recombination sites (ie., Sal I site from the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463) thereby transferring said first segment (ie., the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) from said first nucleic acid molecule to said second nucleic molecule as recited in steps (b) and (c) of claim 44.

Regarding claims 45 and 46, since 3' and 5' of the purified BstE II-Xho I fragment of

pTAC3599 carrying the phoA gene and the appYp-lacz fusion taught by Atlung *et al.*, has restriction sites (see above), Atlung *et al.*, teaches that said first segment (ie., the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) is flanked on one side by said first recombination site and is flanked on the other side by said second recombination site as recited in claim 45 wherein said recombination sites are site-specific recombination sites as recited in claim 46.

Regarding claim 57, since the ligation reaction taught by Atlung *et al.*, is performed in *in vitro* (see Table 1 in page 13 and Figure 2 in page 14), Atlung *et al.*, discloses that said recombination (ie., the ligation taught by Atlung *et al.*,) takes place in vitro as recited in claim 57.

Therefore, Atlung *et al.*, teach all limitations recited in claims 14-20, 27, 32, 33, 44-46, and 57.

Response to Arguments

In page 11 of applicant remarks, applicant argued that "[C]ontrary to the Examiner's above-noted contentions, ligation sites (restriction sites) would not be considered as 'recombination sites' by one of ordinary skill as those terms are used in the present application. As noted above, the presently claimed methods in which recombination proteins are involved are distinct from traditional restriction/ligation cloning. In addition, the recombination proteins that are involved in the methods of the present invention are distinct from ligases.".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. Since "recombination site" was defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by

recombination proteins" (see specification, page 23, last paragraph), ligation sites (restriction sites) can be considered as "recombination sites". Since "recombinant protein" is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph), ligase can be considered as a recombination protein. Based on the definitions of "recombinant protein" and "recombinant protein" in the specification, one of ordinary skill can considered that ligation sites (restriction sites) are "recombination sites" and ligase is a recombination protein.

20. Claims 14-20, 27, 32-51, and 57 are rejected under 35 U.S.C. 102(a) or 102 (e) as being anticipated by Hartley *et al.*, (US Patent No. 5,888,732, filed on June 7, 1996 and published on March 30, 1999).

Hartley *et al.*, teach recombinational cloning using engineered recombination sites.

Regarding claim 14, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Hartley *et al.*, teach a method of making chimeric DNA, which comprises: (a) combining *in vitro* or *in vivo* (i) an Insert Donor DNA molecule, comprising a desired DNA segment flanked by a first recombination site and a second recombination site,

wherein the first and second recombination sites do not recombine with each other; (ii) a Vector Donor DNA molecule containing a third recombination site and a fourth recombination site, wherein the third and fourth recombination sites do not recombine with each other; and (iii) one or more site specific recombination proteins capable of recombining the first and third recombinational sites and/or the second and fourth recombinational sites; thereby allowing recombination to occur, so as to produce at least one Cointegrate DNA molecule, at least one desired Product DNA molecule which comprises said desired DNA segment, and optionally a Byproduct DNA molecule; and then, optionally, (b) selecting for the Product or Byproduct DNA molecule (see column 4, lines 47-67, column 5, line 1, and Figures 1, 2A, 3A, and 4A). Since Hartley *et al.*, teach an Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site, Hartley *et al.*, disclose one or more integration sequences comprising at least one recombination site as recited in claim 14. Since Hartley *et al.*, teach to form at least one Cointegrate DNA molecule in at least one Cointegrate DNA molecule in the presence of an Insert Donor DNA molecule, a Vector Donor DNA molecule, and one or more site specific recombination proteins, Hartley *et al.*, disclose inserting one or more integration sequences comprising at least one recombination site (ie., an Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site) into at least one nucleic acid molecule (ie., the Vector Donor DNA molecule taught by Hartley *et al.*,) as recited in claim 14. Since Hartley *et al.*, teach that, in the presence of a recombinase, the Cointegrate DNA molecule further forms least one desired Product DNA molecule which comprises said desired DNA segment with recombination sites (ie., attR and loxP in Figure 2A) and optionally a Byproduct DNA molecule (see Figures 1 and

2A), Hartley *et al.*, disclose transferring one or more nucleic acid molecules comprising recombination sites (ie., a nucleic acid from the Cointegrate DNA molecule with attR and loxP) into one or more vectors (ie., intprod in Figure 2) in the presence of one or more recombination proteins as recited in claim 14.

Regarding claim 16, since Hartley *et al.*, teach to insert an Insert Donor DNA molecule into a Vector Donor DNA molecule and form at least one Cointegrate DNA molecule in at least one Cointegrate DNA molecule in the presence of one or more site specific recombination proteins wherein the Insert Donor DNA molecule comprises a desired DNA segment flanked by a first recombination site and a second recombination site (see column 4, lines 46-67 and Figures 1, 2A, 3A, and 4A), Hartley *et al.*, disclose inserting one or more integration sequences (ie., the Insert Donor DNA molecule comprises a desired DNA segment flanked by a first recombination site and a second recombination site taught by Hartley *et al.*,), said one or more integration sequences comprising at least one recombination site, into at least one nucleic acid molecule (ie., Vector Donor DNA molecule taught by Hartley *et al.*,) thereby producing a nucleic acid molecule (ie., pEZC7cointegr in Figure 2) comprising at least a first and a second recombination site (ie., attR and loxP); and causing said at least first and second recombination sites to recombine in the presence of at least one recombination protein (ie., Cre in Figure 2) as recited in claim 16.

Regarding claims 15 and 27, since Hartley *et al.*, teach that pEZC726 contains kanamycin resistance gene, Hartley *et al.*, disclose that said nucleic acid molecule is genomic DNA or cDNA as recited in claims 15 and 27.

Regarding claims 17 and 18, since Hartley *et al.*, teach the first and second recombination

sites of pEZC705 (ie., attR and loxP) recombine with the third and fourth recombination sites of pEZC726 (ie., attP and loxP) to form pEZC7 cointegr (see Figure 2A), Hartley *et al.*, disclose that said recombination of said first and second recombination sites results in a circular molecule as recited in claim 17 wherein said first and second recombination sites (ie., att R and loxP) are separated by at least a portion of a nucleic acid as recited in claim 18 (see pEZC705 in Figure 2A).

Regarding claims 19 and 20, since the integration sequences (ie., the Insert Donor DNA molecule such as pEZC705) taught by Hartley *et al.*, has amp (an amplification resistance gene), according to the definition of "selectable markers" in the specification (see page 26, last paragraph bridging to page 27, first paragraph), Hartley *et al., et al.*, disclose that said integration sequence comprises one selectable marker (ie., amp) as recited in claims 19 and 20.

Regarding claims 32-39, since Hartley *et al.*, teach that the first and second recombination sites are attR and loxP respectively (see pEZC7cointegr in Figure 2A), Hartley *et al.*, disclose that said first and second recombination sites are site-specific recombination sites as recited in claims 32 and 33, said recombination sites are selected from the group consisting of loxp, attB, attp, attL, attR, FRT, a recombination site recognized by a resolvase, a bacterial transposable element, an integrating virus, an IS element, a P element of *Drosophila*, a bacterial virulence factor and a mobile genetic element for an eukaryotic organism, or mutants or derivatives thereof as recited in claim 34, said recombination sites are selected from the group consisting of loxP, attB, attP, attL, attR, FRT, a recombination site recognized by a resolvase, a bacterial transposable element, an integrating virus, an IS element, a P element of *Drosophila*, a bacterial virulence factor and a mobile genetic element for an eukaryotic organism as recited in

claim 35, at least one of said first and said second recombination sites is an att site or a mutant or derivative thereof as recited in claim 36, at least one of said first and said second recombination sites is an att site as recited in claim 37, said att site is selected from the group consisting of attB, attP, attL and attR, or a mutant or derivative thereof as recited in claim 38, said att site is selected from the group consisting of attB, attP, attL and attR as recited in claim 39.

Regarding claim 44, since Hartley *et al.*, teach an Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site, Hartley *et al.*, disclose obtaining a first nucleic acid molecule (ie., the Insert Donor DNA) comprising at least a first segment which comprises at least a first and a second recombination site (ie., a desired DNA segment flanked by a first recombination site and a second recombination site) wherein said segment comprises at least one integration sequence as recited in step (a) of claim 44. Since Hartley *et al.*, teach to insert an Insert Donor DNA molecule into a Vector Donor DNA molecule and form at least one Cointegrate DNA molecule in at least one Cointegrate DNA molecule in the presence of one or more site specific recombination proteins capable of recombining the first and third recombinational sites and/or the second and fourth recombinational sites wherein the Vector Donor DNA molecule containing a third recombination site and a fourth recombination site (see column 4, lines 46-67 and Figures 1, 2A, 3A, and 4A), Hartley *et al.*, disclose forming a mixture by mixing said first nucleic acid molecule (ie., the Insert Donor DNA molecule taught by Hartley *et al.*,) with at least one second nucleic acid molecule comprising at least a third and fourth recombination site (ie., the Vector Donor DNA molecule taught by Hartley *et al.*,) in the presence of at least one recombination protein, and incubating said mixture under conditions favoring recombination at least between said first

and third recombination sites and at least between said second and fourth recombination sites, thereby transferring said first segment from said first nucleic acid molecule (ie., see nucleic acid segment from pEZC705 in PEZC7cointegr in Figure 2) from to said second nucleic molecule (ie., the Vector Donor DNA molecule taught by Hartley *et al.,*) as recited in claim 44.

Regarding claim 45, since Hartley *et al.,* teach that there is a nucleic acid segment between attB (ie., a first recombination site) and loxP (ie., a second recombination site), Hartley *et al.,* disclose said first segment is flanked on one side by said first recombination site and is flanked on the other side by said second recombination site as recited by claim 45.

Regarding claims 46-51, since Hartley *et al.,* teach that the first and second recombination sites are attB and loxP respectively (see pEZC705 in Figure 2A), Hartley *et al.,* disclose that said first and second recombination sites are site-specific recombination sites as recited in claim 46, said recombination sites are selected from the group consisting of loxP, attB, attP, attL, attR, FRT, a recombination site recognized by a resolvase, a bacterial transposable element, an integrating virus, an IS element, a P element of *Drosophila*, a bacterial virulence factor and a mobile genetic element for an eukaryotic organism as recited in claim 47, at least one of said first and said second recombination sites is an att site or a mutant or derivative thereof as recited in claim 48, at least one of said recombination sites is an att site as recited in claim 49, said att site is selected from the group consisting of attB, attP, attL and attR, or a mutant or derivative thereof as recited in claim 50, said att site is selected from the group consisting of attB, attP, attL and attR as recited in claim 51.

Regarding claim 57, since the recombination reaction taught by Hartley *et al.,* is

performed in vitro (see column 4, lines 46-67), Hartley *et al.*, disclose that said recombination takes place in vitro as recited in claim 57.

Therefore, Hartley *et al.*, teach all limitations recited in claims 14-20, 27, 32-39, 44-51, and 57.

Response to Arguments

In page 12, second paragraph of applicant's remarks, applicant argues that "[H]artley does not disclose the insertion of one or more integration sequences into at least one nucleic acid molecule. As one of ordinary skill would readily appreciate, the term "integration sequence" as used in the present specification refers to specific mobile genetic elements, i.e., nucleic acid molecules or segments with integrative activity, such as transposons, insertion sequences, integrating virus, homing introns, or other integrating elements, or various combinations thereof. *See, e.g.,* specification at page 34, lines 7-29. Thus, the 'nucleic acid sequence having kam marker' depicted in Figure 2A of Hartley, alleged by the Examiner to be considered as an 'integration sequence' (see Office Action at page 8, lines 15-16), cannot be considered an integration sequence as that term is used in the present specification.".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. According to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph). Since Hartley *et al.*, teach an Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site and Hartley *et al.*, disclose

one or more integration sequences comprising at least one recombination site as recited in claim 14.

21. Claims 14-20, 27, 32-39, 44-51, and 57 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The above patent (US Patent No. 5,888,732) was filed on June 7, 1996 and published on March 30, 1999 and taught all limitations recited in claims 14, 16-20, and 30-43 (see above). However, Gary Temple is not listed in above patent, he can not considered as inventor of this instant application. Please give explanation.

Double Patenting

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 14-20, 27, 32-39, 44-51, and 57 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27-39 of U.S. Patent No.5,888,732. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but examined claims in this instant application are not patentably distinct from the reference claims because the examined claims are either anticipated

by, or would have been obvious over, the reference claims. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969). Although independent claims 14-20, 27, 32-39, 44-51, and 57 in this instant application are not identical to claims 27-39 of U.S. Patent No.5,888,732, 27-39 of U.S. Patent No.5,888,732 are directed to the same subject matter and fall entirely within the scope of claims 14-20, 27, 32-39, 44-51, and 57 in this instant application. In other words, claims 14-20, 27, 32-39, 44-51, and 57 in this instant application are anticipated by claims 27-39 of U.S. Patent No. 5,888,732.

Response to Arguments

In page 14, third paragraph of applicant's remarks, applicant argues that, "[F]or the reasons discussed above distinguishing the presently claimed invention from the disclosure of Hartley, Applicants respectfully disagree with the Examiner's contention that the claims of the present invention are not patentably distinct from claim 29 of Hartley.".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. According to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph).

24. Since claims 27-39 of U.S. Patent No. 5,888,732 teach an Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site and claims 27-39 of U.S. Patent No. 5,888,732 disclose one or more integration sequences comprising at least one recombination site as recited in claims 14 and 16.

Conclusion

25. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

(1) The prior art that can be used for rejections under 35 U.S.C. 102(e) or 102(f) and double patenting:

Hartley et al., (U.S. Patent Nos. 6,171,861 B1, 6,270,969, and 6,277,608)

(2) The prior art that can be used for rejections under 35 U.S.C. 102(e) or 102(f):

Hartley et al., (U.S. Patent No. 6,143,557)

26. No claim is allowed.

27. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
March 22, 2004

FRANK LU
PATENT EXAMINER